ORIGINAL ARTICLE

CD4 CHANGES IN HAART-NAÏVE HIV POSITIVE PREGNANT WOMEN ON HAART: LOW RESOURCE SETTING EXPERIENCE.

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ABSTRACT

PURPOSE: PMTCT interventions, especially initiation of Highly active antiretroviral therapy (HAART) has modified the natural history of HIV infection by reducing both peripartal and neonatal HIV infections, but the pattern of the immunologic responses of these pregnant women to HAART remains speculative. It is hoped from this study, to describe the pattern of immunologic response of naïve, HIV positive pregnant women on their first initiation on HAART.

METHODS: This study described the pattern of CD4 changes observed in freshly diagnosed 126 HIV positive pregnant women, stratified into the trimesters of pregnancy and commenced on HAART (Zidovudine, Lamivudine and Nevirapine) for a period of 2 months in pregnancy. CD4 counts were determined at point of recruitment and monthly thereafter using a Parteccytometer counter (Cyflow$^{(R)}$). Neonatal outcome was also described.

RESULTS: Our findings suggest better immunologic response and fewer neonatal infectionsin group of naïve women initiated on HAART while in the first 26 weeks of pregnancy and lesser response in those commenced in the third trimester of pregnancy.

CONCLUSION: Concerted efforts should be directed towards the initiation of HAART prophylaxis before end of 2nd trimester of pregnancy.

Keywords: PMTCT, pregnant women, HAART, CD4 changes

INTRODUCTION

It is well known that the introduction and widespread use of highly active antiretroviral therapy (HAART) has modified the natural history of HIV infection.Significantly, PMTCT practices remain very effective public healthinterventionsin improving maternal health, as well as reducing both peripartal and neonatal HIV infections [1, 2]. While, attempts had been made in general HIV positive patients to characterise both immunologic and virologic responses in patients on HAART in developed countries, such attentions have not been focussed on HIV positive pregnant population, more especially, in our environment with high HIV infection burden. We found no record in our environment of any description of the pattern of immunologic responses of pregnant HIV positive women on antiretroviral drugs. Thus it becomes highly imperative for such, considering the hitherto immunologic changes expected of normal pregnancy. This study thus attempt an assessment of the pattern of immunologic (CD4) changes in naïve HIV positive pregnant women, in the first two months of commencing HAART, with a view to possibly postulate CD4 response rate and recommend the ideal time to initiate HAARTin HIV positive pregnant patients.

METHODOLOGY

Patients with double positive parallel rapid test results at EGA 12 - 28 weeks at LAUTECH Teaching Hospital, Osogbo, Nigeria in the year 2008/2009 were prospectively enrolled into the study and stratified into the 3groups by the trimesters of pregnancy. Institutional Ethical approval was obtained for the study. All patients recruited gave consent and had venous blood samples collected into EDTA bottle for CD4 count (cells/µl) at point of recruitment and monthly thereafter using a Partec cytometer counter (Cyflow$^{(R)}$), among other pre-requisite investigations for monitoring in ARV therapy. Each patient was prescribed combination of Highly Active Antiretroviral Therapy (HAART) of tablets of Zidovudine 300mg twice daily, Lamivudine 150mg twice daily and Nevirapine200mg daily first two weeks, thereafter 200mg twice daily according to the National guideline[1]. Patients with Haemoglobin level <8g/dl, concomitant Hepatitis C or any opportunistic infections, illicit drug/alcohol use were excluded

from the study. Biochemical monitoring was as prescribed in the National guideline for PMTCT (Nigeria). Data obtained were analysed for descriptive statistics using SPSS 17 statistical package, percentage difference of mean of the CD4 counts, stratified by trimesters of pregnancy determined and ANOVA for difference of means between groups at initiation of HAART and at 4th and 8th week respectively.

RESULTS

A total of 126 patients were recruited over the 2 years period. The overall mean age (Years), Parity and EGA (Weeks) was 29.73 $\pm$ 4.42, 1.52 $\pm$ 1.41 and 19.96 $\pm$ 4.20 respectively.

TABLE I: DEMOGRAPHY OF PATIENTS

	N	Minimum	Maximum	Mean	Std. Deviation
AGE (Years)	126	20.00	40.00	29.73	4.42
PARITY	126	.00	5.00	1.52	1.41
EGA (Weeks)	126	12.00	28.00	19.96	4.20

In the 1st trimester group $Mean^0$ CD4 = 408.75 cells/μL (223.70), C.I = 221.73, 595.77, $Mean^1$ = 544 cells/μL (224.90), C.I = 355.98, 732.02, and $Mean^2$ = 626.63 cells/μL (247.27), C.I = 419.90, 833.00. The counts in the 2nd trimester group are, $*Mean^0$ = 367.07 cells/μL (202.67), C.I = 202.67, 328.95, $*Mean^1$ = 489.41 cells/μL (173.23), C.I = 456.82 – 521.99, $*Mean^2$ = 560.43 cells/μL (154.56), C.I = 531.36, 589.51. The 3rd trimester group's parameters are as follows: $**Mean^0$ = 540.14 cells/μL (188.86), C.I = 365.48, 714.81, $**Mean^1$ = 607.14 cells/μL (164.22), C.I = 164.22, 455.27, $**Mean^2$ = 650.26 cells/μL (163.85), C.I = 498.75, 801.82. The overall mean CD4 change in the 2 months of study in the three trimesters groups are 217, 192.93 and 110.12cells/μL (P = 0.088, 0.179, 0.217) respectively, while the percentages differences of Mean of the CD4 counts in between points of evaluation for each trimester are: 33.09% & 15.19% (1st trimester), 33.33% & 14.51% (2nd trimester) and 12.38% & 7.13% (3rd trimesters) respectively.

TABLE II: DISTRIBUTION OF PATIENTS BY TRIMESTERS OF PREGNANCY

Trimesters	Age (Years) Mean (SD)	Parity Range (Median)	EGA (Weeks) Mean (SD)
1st Trimester	28.750 (4.683)	0 – 2 (1)	12.750 (0.463)
2nd Trimester	29.982 (4.464)	0 – 5 (1)	20.027 (3.602)
3rd Trimester	26.857 (2.340)	0 – 4 (3)	27.143 (0.378)

TABLE III: AVERAGE CD4 COUNTS OF PATIENTS AT RECRUITMENT AND MONTHLY

Trimesters	Mean $CD4^0$ (C.I) cells/μL	Mean $CD4^1$ (C.I) cells/μL	Mean $CD4^2$ (C.I) cells/μL
First	408.75 (221.73, 595.77)	544.00 (355.98, 732.02)	626.63 (419.90, 833.00)
Second	367.07 (202.67, 328.95)	489.41 (456.82, 521.99)	560.43 (531.36, 589.51)
Third	540.14 (365.48, 714.81)	607.00 (164.22, 455.27)	650.26 (498.75, 801.82)
P-value	0.088	0.179	0.217

DISCUSSION

Highly Active Antiretroviral Therapy (HAART) - typically composed of 3 antiretroviral agents from 2 drug classes - has substantially reduced MTCT rates through successful suppression of HIV RNA load[1, 2]. This fact has been established in many collaborative studies and therefore formed the basis of the recommendation for the HAART prophylaxis in HIV positive pregnant women, irrespective of the CD4 count levels[1, 3, 4]. It is therefore a well-known fact that responses to antiretroviral drugs (ARVs) are both virologic (HIV RNA load) and immunologic (CD4 count).

In this study we described the pattern of CD4 changes observed in freshly diagnosed HIV positive pregnant women,across the trimesters, in our Institution, who were commenced on HAART

(Zidovudine, Lamivudine and Nevirapine) for a period of 2 months in pregnancy.

Our findings showednumerically, but statistically insignificant, higher immunologic response in group of naïve women initiated on HAART while in the first 26 weeks of pregnancyand lesser response in those commenced in the third trimester of pregnancy (Table IV).

TABLE IV: CALCULATED PERCENTAGE DIFFERENCE OF MEANS BY TRIMESTERS OF PREGNANCY

Trimesters	% Difference of Means[1] (At 0 – 4th week)	% Difference of Means[2] (4th - 8th week)
First Trimester	33.09%	15.19%
Second Trimester	33.33%	14.51%
Third Trimester	12.38%	7.13%

Key:

$CD4^0$ -   CD4 at commencement of HAART

$CD4^1$ -   CD4 at 4 weeks of commencement of HAART

$CD4^2$ -   CD4 at 8 weeks of commencement of HAART

C.I   -   95% Confidence Interval

Difference of Means[1]   -   Difference between initiation & 4 weeks of HAART

Difference of Means[2]   -   Difference between 4th weekand 8th week of HAART

The might not be un-related to the adaptive immunology of pregnancy, whereby, elevated levels of progesterone and estrogen, greatest during the first half of pregnancy, lead to an increase in CD4+ , CD25+ regulatory T cells and tolerance to alloantigens such as fetal antigens[5, 6]. The effect of pregnancy on regulatory T cells could possibly lead to a better virologic response to HAART in women first experiencing HAART during pregnancy. If this be the case, we can at least exploit this natural advantage and strive to initiate HAART in HIV positive pregnant women in the first half of pregnancy at the latest. It is incontrovertible, that opportunistic infection, AIDS related complications and consequently risks of mother-to-child infections are much less with adequate defence confer by good CD4 [7]. However, some other studies, comparing CD4 changes in HIV-1 positive pregnant women, had reported that women have lower CD4 cell counts changes during pregnancy than in the postpartum period [8].Few studies have actually described CD4 changes in pregnant women on HAART and even in those studies, it was comparison of the changes in pregnancy with the postpartum period [9]

In our patients' population, the mean CD4 counts of the 3rd trimester group was the highest at diagnosis and enrolment, but only improved by percentage difference of 12.38% and 7.13% in the two subsequent 4 weekly interval, compared with 33.09% and 15.19% (1st trimester group) and 33.33% and 14.51% (2nd trimester group) respectively. However, a consistent finding across the groups is progressive decline in increment in means as the weeks increase (Table IV).

Although we controlled and excluded important baseline characteristics that are associated with immune recovery (illicitdrug use [10] and hepatitis C virus co-infection[11]), other factors such as baseline CD4+ lymphocyte count, duration of HIV infection and HIV-1 viral load, CD4+ lymphocyte count nadir [12] could not be excluded. Some other inherent limitations preclude causal inferences from this study. First, being that the study is observational in nature. Also, the patients are not evenly distributed across groups, third is the time limit conferred by the duration of pregnancyand lastly, perhaps most important is the inability, due to limited resources in our setting, to concurrently assess the viral load and correlate with the CD4 count. It must however be stated that WHO and National guideline, due to this resources limitation recommended CD4 counts for response monitoring in HIV patient on ARV[13, 1].

In this study, we recorded 2 perinatal deaths and 4 HIV neonatal infections by the 6th month of follow-up (vertical transmission rate of 3.17%), 3 of which occurred in the women enrolled in the 3rd trimester and 1 in the 2nd trimester, while both perinatal deaths were due to severe asphyxia. All the women in whom neonatal infections were recorded breastfed their babies and were continuing prophylactic HAART.

It is however, noteworthy, that possibly because of exclusion of other co-infections – HCV and other opportunistic infections, as well as drug and alcohol abuse, most of the patients had above 400 CD4 from 4th week of HAART initiation.

With the above noted, this study found a better immunologic response among HIV positive, ARV naïve women who started HAART during the first 26 weeks of pregnancy compared to women who started HAART in the last 13 weeks, though a causal relationship could not be established due to the low power of this study. However, in our opinion, this might pose great clinical challenges in our environment where late antenatal care booking is the norm. At the moment, HAART's response monitoringin our environment is limited to Immunologic parameter (CD4 count) only, with just very few research centres having the capacity to undertake virologic monitoring.

It is hereby summated that there might bebetter immunological response in ARV naïve HIV positive pregnant women when commenced on HAART in the first 26 weeks of pregnancy, as progressive decline in CD4 increase was observed as the pregnancy advanced across the trimester, with the least immunological response and more neonatal infection observed in 3rd trimester group. Public health enlightenment should utilize this information and efforts should be directed to the initiation of HAART prophylaxis before end of 2nd trimester of pregnancy.Larger studies with concurrent viral load assessment are however recommended to further explore causal relationship of these factors.

CONFLICT OF INTEREST NOTIFICATION:

We declare that we have no conflict of interest; no funding/grant was received for this study and no commercial relationship.

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